REMARKS

Claims 54-70 are pending. Claims 60 and 61 have been canceled without prejudice. Claim 54 has been amended to remove the reference to non-elected subject matter. Claims 55-59 and 62-69 have been amended to address minor formatting issues. Applicants submit that these amendments raise no issue of new matter. Thus, claims 54-59 and 62-70 will be pending and under examination upon the entry of this Amendment.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the July 16, 2003 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

Information Disclosure Statement

The Examiner noted that the form PTO-1449 and the copies of the references submitted in connection with applicants' February 27, 2002 Supplemental Information Disclosure Statement are missing. The Examiner stated that applicant may submit the PTO-1449 and the references for consideration.

In response, applicants submit herewith as **Exhibit A** a copy of their February 27, 2002 Supplemental Information Disclosure Statement, including Form PTO-1449, Supplementary Partial European Search Report, PCT International Publication No. WO 97/11607, a copy of a check for $180.00, and a copy of the stamped postcard indicating receipt of these items by the U.S. Patent and Trademark Office.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 54-57 and 62-70 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

In particular, the Examiner alleges that the claims are not enabled for "any agent" which inhibits an immune response costimulation event.

In response, applicants respectfully traverse and maintain that the instant specification enables the claimed method. In support, applicants rely on the high level of skill in the art, the working examples in the specification, and the particularity of the event itself, which necessarily limits the range of possible inhibitors.

As defined in the specification at page 27, an "immune-system costimulation event" is an interaction between an APC and a T-cell, including any specific binding of an APC cell-surface molecule, other than an MHC-bound antigen, to a specific ligand on a T-cell. As further taught in the specification and the prior art, the APC:T-cell interaction that results in the costimulation event is that between the B7 molecule on the APC and either CD28 or CTLA4 on the T-cell. Specific examples of inhibitors of this interaction were known in the art and are described in the specification, e.g., anti-B7 monoclonal antibodies (Lenschow p. 790), CTLA4Ig, CD28Ig, and B7Ig (Linsely at col. 14, 17).

In view of the above remarks, applicants maintain that claims 54-57 and 62-70 satisfy the requirements of U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 54-57 and 62-70 under 35 U.S.C. §103(a) as allegedly unpatentable over Lenschow in view of Goosen, Soon-Shiong, Akalin, Linsley, Padrid, and Steurer.

In response, applicants respectfully traverse the Examiner's rejection.

To establish a prima facie case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, that there is a suggestion or motivation to combine the reference teachings. Second, that there is a reasonable expectation of

success, and third, that the combined references teach or suggest every element of the claim.

Applicants maintain that the cited references fail to support a *prima facie* case of obviousness for reasons of record and for the additional reasons set forth below.

There is no suggestion in the references themselves to combine the elements of microencapsulation and CTLA4Ig in a method of cell or tissue transplantation. Instead, the Examiner relies upon his view of the knowledge generally available to one of ordinary skill in the art to provide both the suggestion and motivation to combine the teachings of the cited references, as well as the expectation of success in making said combination. Applicants maintain that the Examiner's line of reasoning as to why the artisan would have found the claimed invention obvious in light of the teachings of the cited references is improper because it is based on impermissible hindsight and an "obvious to try" rationale.

The Examiner alleges that since CTLA4Ig inhibits immune responses and since microencapsulation is impermeable to immune system proteins while protecting the graft from contact with host effector cells, the combination of CTLA4Ig and microencapsulation in order to provide enhanced graft protection is obvious.

Applicants maintain that absent the teachings of the instant specification, one of skill in the art would not have expected CTLA4Ig to have a significant effect on the survival of an encapsulated graft. Applicants submit that the motivation to combine microencapsulation with CTLA4Ig originates in the instant discovery that host B7+APC:T-cell interaction is the dominant factor driving the destruction of the encapsulated graft. CTLA4Ig was known in the art as a specific inhibitor of this pathway (see Lenschow p. 789-90). In finding the claimed methods obvious, the Examiner ignores the high degree of uncertainty in the art at the time of filing with respect to the cause of graft destruction where microencapsulation prevented contact between host effector cells and graft cells.

The specification teaches this uncertainty regarding the mechanism of encapsulated graft destruction beginning at page 8. A number of theories that had been posited in the prior art are set forth therein. For example, cytotoxic factors were posited to permeate the capsule membrane, causing graft destruction. Such factors were known to be produced by host immune cells such as natural killer cells, cytotoxic T-lymphocytes, and macrophages (Soon-Shiong at 218, and the specification at page 8, lines 23-32). Another possibile source of cytotoxic factors was from xenogeneic macrophages within the graft itself (see page 9, lines 14-34). Finally, the specification teaches that T-helper cells were suspected in the rejection of encapsulated grafts (see page 9, lines 1-12). However, absent the teachings of the instant disclosure, the prior art provides nothing more than a general approach toward what seemed like a promising field of experimentation, i.e., inhibition of APC:T-cell interaction, among a number of other, equally promising directions, i.e., inhibition of toxin release by natural killer cells, cytotoxic T-lymphocytes, and macrophages, or improvements in capsule design to protect the graft from such cytotoxic factors.

Applicants further submit that the prior art teaches away from combining CTLA4Ig with microencapsulation. Although Lenschow demonstrates improved xenogeneic graft survival by treatment with CTLA4Ig, Lenschow strongly supports the view that the immune response to the graft involves direct presentation of xenogeneic antigens by *graft APCs* (Lenschow at 790-91). In other words, following the teachings of Lenschow, the artisan would be motivated to inhibit the interaction between host T-helper cells and graft APCs. Since this is accomplished by the physical barrier of the microcapsule itself, there is no reason to also administer CTLA4Ig where the graft is encapsulated. Moreover, while acknowledging the possibility that host B7+APCs might be involved in xenograft rejection, Lenschow proceeds to teach away from this possibility by offering another explanation for the inability of the anti-B7 MAb to block rejection as effectively as CTLA4Ig, namely, inadequate antibody dosage (Lenschow at 791).

None of the remaining references, when combined with Lenschow and Soon-Shiong, overcome this deficiency of motive and expectation of success in combining CTLA4Ig (or other blocker of the B7+APC-dependent activation of T-helper cells) with microencapulation to enhance xenogeneic graft survival. Goosen teaches microencapsulation of living cells, but does not teach anything about the efficacy of the microcapsule in preventing the cell-mediated immune response to such cells. The remaining references all teach the effectiveness of CTLA4Ig in inhibiting cell-mediated graft rejection, but none addresses the role of graft versus host B7+APCs in a xenogenic model that would suggest combining CTLA4Ig with microencapsulation, particularly in view of the strong suggestion to the contrary provided by Lenschow.

Thus, contrary to the Examiner's assertion at page 6, the advantages of combining CTLA4Ig with microencapsulation do not flow naturally from following the suggestion of the prior art, and in fact the prior art teaches away from this combination. Moreover, in view of the uncertainty in the art, applicants maintain that the Examiner has engaged in impermissible hindsight by reading the knowledge gleaned from applicants' disclosure into the Examiner's view of the state of the art. Finally, in view of the fact that the APC:T-helper cell interaction targeted by the claimed methods was but one of many possible targets available to the skilled artisan, applicants maintain that the Examiner has applied an improper "obvious to try" standard in rejecting the claimed combination. Applicants submit that the prior art provides nothing more than a general approach toward what seemed like a promising field of experimentation. The Examiner has not demonstrated otherwise.

In view of the above remarks, applicants maintain that the rejected claims satisfy the requirements of 35. U.S.C. § 103.

Summary

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $55.00 fee, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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